# Reduction of Cardiovascular Events by Simvastatin in Nondiabetic Coronary Heart Disease Patients With and Without the Metabolic Syndrome

## Subgroup analyses of the Scandinavian Simvastatin Survival Study (4S)

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**OBJECTIVE** — To assess the effect of simvastatin treatment on the risk of cardiovascular events in nondiabetic patients with coronary heart disease (CHD) with and without the metabolic syndrome, as defined by the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP-III).

**RESEARCH DESIGN AND METHODS** — Subgroup analyses were performed on data from 3,933 nondiabetic patients with clinically established CHD, serum total cholesterol level 5.5–8.0 mmol/l, and serum triglyceride level ≤2.5 mmol/l who were participating in the Scandinavian Simvastatin Survival Study (4S), a randomized, placebo-controlled trial. End points were total mortality, coronary mortality, major CHD event, myocardial revascularization, any CHD event, stroke, and any atherosclerotic event.

**RESULTS** — Over the 5.4-year median follow-up period, simvastatin produced similar changes in serum lipid levels in 893 patients with the metabolic syndrome and in 3,040 patients without the metabolic syndrome. The relative risks of main end points in simvastatin-treated patients compared with placebo-treated patients with the metabolic syndrome were as follows: total mortality 0.54 (95% CI 0.36–0.82), coronary mortality 0.39 (0.23–0.65), major CHD event 0.59 (0.45–0.77), and any atherosclerotic event 0.69 (0.56–0.84). The corresponding RRs in patients without the metabolic syndrome were 0.72 (0.56–0.91), 0.62 (0.45–0.84), 0.71 (0.61–0.82), and 0.76 (0.68–0.85).

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**CONCLUSIONS** — Nondiabetic CHD patients with or without the metabolic syndrome realize from simvastatin treatment a similar, substantial relative reduction in the risk of cardiovascular events. The absolute benefit may be greater in patients with the metabolic syndrome because they are at a higher absolute risk.

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T he metabolic syndrome, also called insulin resistance syndrome, is a clustering of several risk factors, including obesity and its central distribution, impaired glucose regulation, elevated triglycerides, decreased HDL cholesterol, and elevated blood pressure (1,2). Insulin resistance is considered to be the underlying cause of the syndrome, but its pathogenesis is still incompletely understood. Since the metabolic syndrome is associated with the risk of development of type 2 diabetes and atherosclerotic cardiovascular disease, it has become the subject of intensive research interest. This research has, however, suffered from the diversity in the definition of the syndrome. To achieve better uniformity, the World Health Organization (WHO) (3) and the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP-III) (4) have recently formulated definitions for the metabolic syndrome. The individual risk factor components of the syndrome and cutoffs used for them differ in some respects between these two definitions.

Defined by either the WHO or NCEP definition, the prevalence of the metabolic syndrome increases markedly with age (5–7). In the U.S., 24% of the adult population older than 20 years have the metabolic syndrome, and in individuals older than 50 years of age, its prevalence rises to >40% (5,8). There are, however,

substantial differences in the prevalence of the syndrome between ethnic groups and also between populations with similar ethnic and cultural origin (6,7,9).

Several prospective epidemiologic studies have confirmed, either using the WHO or the NCEP definition, that the presence of the metabolic syndrome is associated with an increased all-cause and cardiovascular mortality (7,10–12) and incidence of coronary heart disease (CHD) and stroke (13). The importance of the metabolic syndrome as a predictor of risk of CHD events has also been examined in the placebo groups of three large trials of statin treatment for CHD prevention: the West of Scotland Coronary Prevention Study (WOSCOPS) (14), the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS), and the Scandinavian Simvastatin Survival Study (4S) (15). In these studies, the presence of the metabolic syndrome at baseline was associated with a clear increase in the risk of CHD events in placebo-treated patients; the increase was 1.8-fold in the WOSCOPS, 1.4-fold in the AFCAPS/TexCAPS, and 1.5-fold in the 4S (14,15). In the AFCAPS/TexCAPS and 4S placebo groups, the presence of the metabolic syndrome increased the risk of CHD events over and above the prediction obtained from the Framingham risk score. In the present study, based on a subgroup analysis of the 4S, we assessed the reduction in the risk of CHD events achieved by simvastatin treatment compared with placebo in nondiabetic CHD patients with and without the metabolic syndrome.

## RESEARCH DESIGN AND METHODS — The 4S was a randomized, double-blind, placebo-controlled clinical trial of simvastatin therapy in patients with established CHD and elevated total cholesterol performed in 94 centers in Denmark, Finland, Iceland, Norway, and Sweden. The design, organization, and practical aspects of the trial and the main findings on mortality and morbidity have been described in detail previously (16,17). The study protocol was approved by regional or national ethics committees, as appropriate, in each of the participating countries.

The 4,444 patients (3,459 men and 985 women) participating in the 4S were aged 35–70 years and had either previous myocardial infarction (MI) or angina pec-

toris. At randomization, total cholesterol levels were between 5.5 and 8.0 mmol/l and triglyceride levels were ≤2.5 mmol/l. The initial dosage of simvastatin was 20 mg daily, and it was titrated to 40 mg daily in patients who did not reach the target total cholesterol level of 3.0–5.2 mmol/l after 6–18 weeks by using methods that preserved the study blinding. Median follow-up was 5.4 years (range for those surviving, 4.9–6.3 years). The primary end point was total mortality. Major coronary events (coronary death, definite or probable hospital-verified nonfatal MI, resuscitated cardiac arrest, and definite silent MI verified by electrocardiography) formed the secondary end point. Tertiary end points included *1*) any CHD event (a major coronary event or hospital admission for acute coronary event without the diagnosis of MI, mainly prolonged chest pain); *2*) any atherosclerotic cardiovascular disease event (death from or hospitalization for such an event or myocardial revascularization procedure [either coronary artery bypass grafting or coronary angioplasty], or cerebrovascular or peripheral vascular disease event); and *3*) myocardial revascularization procedure.

Patients with previously diagnosed diabetes (*n* = 202) and patients with undiagnosed diabetes with fasting plasma glucose (FPG) ≥7.0 mmol/l at baseline examination (*n* = 281) were excluded from the present subgroup analyses. Among the remaining nondiabetic patients, those patients who fulfilled three or more of the following modified NCEP criteria were identified as having the metabolic syndrome: BMI ≥30 kg/m$^2$ (substitute for waist circumference); triglycerides ≥1.69 mmol/l; HDL cholesterol <1.04 mmol/l in men and <1.29 mmol/l in women; blood pressure ≥130/85 mmHg and/or previously diagnosed hypertension and/or reported antihypertensive medication use; and FPG ≥6.1 and <7.0 mmol/l.

### Statistical analysis
The effect of simvastatin versus placebo was assessed by calculating, with the Cox proportional hazards model, the relative risks and 95% CIs for the study end points within the subgroups of patients with and without the metabolic syndrome. Analyses were based on time to first event for each end point analyzed. The Cox proportional hazards model included the following factors: treatment

(simvastatin or placebo), subgroup (with or without the metabolic syndrome at baseline), interaction term for treatment by subgroup, stratification by age (<60 vs. ≥60 years), and sex. Number of events and incidence rates, presented as the number of events per 100 patient-years, were provided by treatment and subgroup.

Baseline demographics and characteristics are reported as means ± SD, unless otherwise specified. Treatment effects on lipid parameters were expressed as percent change from baseline to 1 year of treatment.

## RESULTS — Of the 4,444 randomized patients in 4S, 3,961 did not have diabetes and 3,933 had sufficient data to determine metabolic syndrome status. Of the 3,933 patients, 893 (22.7%) fulfilled the criteria for the metabolic syndrome; 423 were in the simvastatin group and 470 were in the placebo group. The baseline characteristics of the patients with and without the metabolic syndrome are shown in Table 1. No differences were observed between these patient groups for age, total cholesterol, and LDL cholesterol. As expected, patients with the metabolic syndrome had increased BMI, systolic and diastolic blood pressure, FPG, triglyceride level, non-HDL cholesterol level, and apolipoprotein B and decreased HDL cholesterol level and apolipoprotein A-I. By design, the percentage of patients fulfilling criteria for the individual components of the metabolic syndrome (BMI, 28 vs. 4%; hypertension, 95 vs. 72%; FPG, 39 vs. 11%; triglycerides, 81 vs. 17%; HDL cholesterol, 83 vs. 24%) was greater for patients with the metabolic syndrome compared with those without the syndrome, respectively. Of the 893 patients with the metabolic syndrome, the proportion of patients presenting with three, four, or five criteria of the syndrome was 77.8, 18.4, and 3.8%, respectively. The combination of hypertension, high triglyceride level, and low HDL cholesterol level was noted in 61.4% of the patients with the metabolic syndrome. Hypertension, low HDL cholesterol level, and impaired FPG as well as hypertension, high triglyceride level, and impaired FPG were the next most common combinations leading to the diagnosis of the syndrome.

Treatment with simvastatin significantly reduced LDL cholesterol and tri-

**Table 1—*Baseline characteristics of patients with and without the metabolic syndrome***

| | Metabolic syndrome present | Metabolic syndrome absent |
|---|---|---|
| *n* | 893 | 3,040 |
| Age (years) | 58 ± 7 | 59 ± 7 |
| Men (%) | 79 | 82 |
| BMI (kg/m$^2$) | 28 ± 4 | 25 ± 3 |
| Systolic blood pressure (mmHg) | 142 ± 18 | 137 ± 20 |
| Diastolic blood pressure (mmHg) | 86 ± 9 | 83 ± 9 |
| FPG (mmol/l) | 5.8 ± 0.7 | 5.4 ± 0.6 |
| Total cholesterol (mmol/l) | 6.78 ± 0.67 | 6.72 ± 0.67 |
| LDL cholesterol (mmol/l) | 4.91 ± 0.67 | 4.86 ± 0.65 |
| Triglycerides (mmol/l) | 1.95 ± 0.44 | 1.34 ± 0.42 |
| HDL cholesterol (mmol/l) | 0.98 ± 0.18 | 1.24 ± 0.29 |
| Non-HDL cholesterol (mmol/l) | 5.79 ± 0.67 | 5.48 ± 0.70 |
| Apolipoprotein B (g/l) | 1.25 ± 0.16 | 1.13 ± 0.17 |
| Apolipoprotein A-I (g/l) | 1.22 ± 0.17 | 1.30 ± 0.22 |

Data are means ± SD, unless otherwise indicated.

glycerides and increased HDL cholesterol after 1 year (Fig. 1). Total cholesterol and non-HDL cholesterol were also significantly reduced with simvastatin after 1 year by ~28 and 35%, respectively, for both subgroups. At the end of the study, mean percent changes from baseline (placebo adjusted) were also similar between the simvastatin-treated patients with and those without the metabolic syndrome for LDL cholesterol, triglycerides, and HDL cholesterol (−35, −17, and +7%, respectively) and also to those of simvasta-tin-treated patients in the whole 4S cohort (18).

Table 2 shows crude incidence rates of end point events in simvastatin- and placebo-treated patients with and without the metabolic syndrome. Placebo-treated patients with the metabolic syndrome had increased incidence rates compared with placebo-treated patients without the syndrome for all event types except stroke. Regardless of subgroup, compared with placebo, treatment with simvastatin significantly reduced event rates for all event types except stroke. The effect of simvastatin treatment is evident in the relative risk estimates for simvasta-tin versus placebo within subgroups of patients with and without the metabolic syndrome consistently across all events (Fig. 2). Although relative risk reduction with simvastatin seems to be greater in the subgroup of patients with the metabolic syndrome (31–61% across the seven end points) compared with those without the metabolic syndrome (24–38%), the differences between subgroups were not statistically significant (treatment-by-subgroup interaction, $P > 0.12$ for each event type). Because the absolute risk of all types of events was, however, higher in patients with the metabolic syndrome than in those without it (Table 2), calculations of the absolute treatment benefit from simvastatin in terms of the number needed to treat (NNT) gave smaller NNTs for patients with the metabolic syndrome than for those without it. To prevent a major coronary event in a year, the NNT is 34 for patients with the metabolic syndrome and 63 for patients without the syndrome. Similar differences for NNT were obtained for total mortality (84 vs. 194), coronary mortality (76 vs. 199), myocardial revascularization (56 vs. 92), any CHD event (30 vs. 43), stroke (321 vs. 422), and any atherosclerotic event (26 vs. 39) in patients with the metabolic
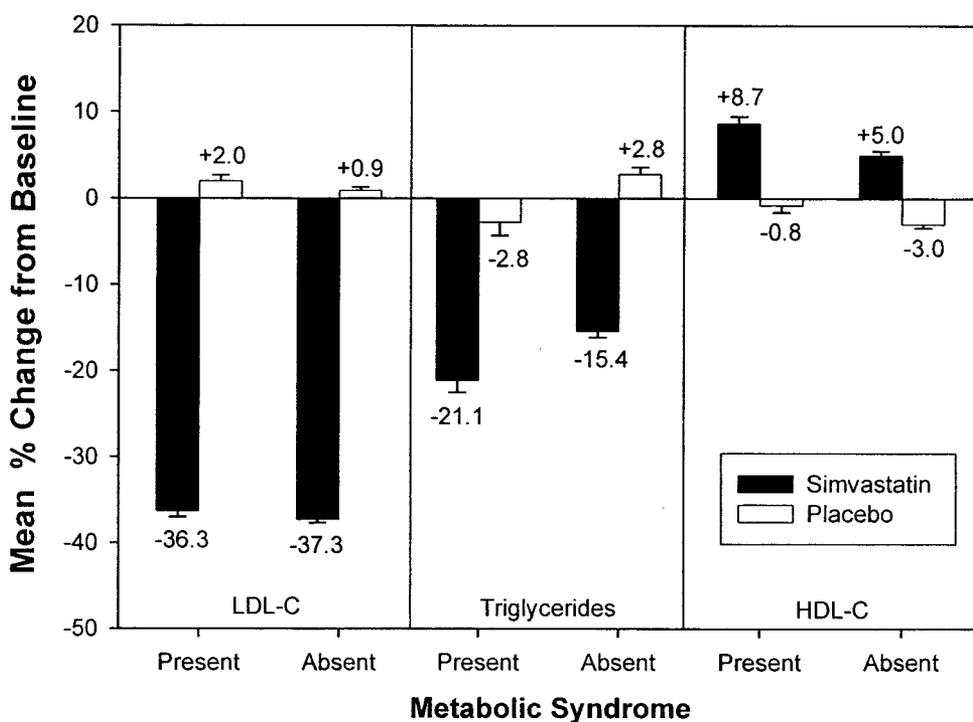


**Figure 1—***Mean percent change in lipid parameters in nondiabetic CHD patients with or without the metabolic syndrome after treatment with simvastatin (■) or placebo (□) for 1 year. Data are means ± SE.*

**Table 2—***Incidence rates of CHD events in patients with or without the metabolic syndrome on simvastatin or placebo*

| End point event and group | n/N (%) | | Event rates/100 patient-years | | Difference from placebo | 95% CI for difference |
|---|---|---|---|---|---|---|
| | SIMVA | PBO | SIMVA | PBO | | |
| Total mortality | | | | | | |
| MetS present | 35/423 (8.3) | 66/470 (14.0) | 1.57 | 2.77 | −1.20 | −2.04 to −0.35 |
| MetS absent | 111/1,532 (7.3) | 149/1,508 (9.9) | 1.37 | 1.89 | −0.52 | −0.91 to −0.12 |
| Coronary mortality | | | | | | |
| MetS present | 20/423 (4.7) | 53/470 (11.3) | 0.90 | 2.22 | −1.32 | −2.04 to −0.61 |
| MetS absent | 68/1,532 (4.4) | 106/1,508 (7.0) | 0.84 | 1.34 | −0.50 | −0.83 to −0.18 |
| Major coronary event | | | | | | |
| MetS present | 87/423 (20.6) | 150/470 (31.9) | 4.35 | 7.32 | −2.97 | −4.45 to −1.48 |
| MetS absent | 282/1,532 (18.4) | 380/1,508 (25.2) | 3.80 | 5.38 | −1.58 | −2.28 to −0.88 |
| Revascularization | | | | | | |
| MetS present | 48/423 (11.4) | 87/470 (18.5) | 2.29 | 4.07 | −1.78 | −2.85 to −0.71 |
| MetS absent | 174/1,532 (11.4) | 246/1,508 (16.3) | 2.29 | 3.38 | −1.09 | −1.63 to −0.55 |
| Any CHD event | | | | | | |
| MetS present | 137/423 (32.4) | 202/470 (43.0) | 7.57 | 10.89 | −3.32 | −5.28 to −1.35 |
| MetS absent | 481/1,532 (31.4) | 602/1,508 (39.9) | 7.13 | 9.45 | −2.32 | −3.31 to −1.34 |
| Stroke | | | | | | |
| MetS present | 11/423 (2.6) | 19/470 (4.0) | 0.50 | 0.81 | −0.31 | −0.78 to 0.16 |
| MetS absent | 48/1,532 (3.1) | 65/1,508 (4.3) | 0.60 | 0.84 | −0.24 | −0.50 to 0.03 |
| Any atherosclerotic event | | | | | | |
| MetS present | 152/423 (35.9) | 223/470 (47.5) | 8.46 | 12.28 | −3.82 | −5.92 to −1.72 |
| MetS absent | 536/1,532 (35.0) | 666/1,508 (44.2) | 8.04 | 10.62 | −2.58 | −3.63 to −1.52 |

MetS, metabolic syndrome; PBO, placebo; SIMVA, simvastatin.

syndrome compared with those without it, respectively.

**CONCLUSIONS** — These post-hoc subgroup analyses of the 4S data provide evidence that, in terms of relative risk reduction, simvastatin treatment reduces the risk of all-cause mortality, major CHD events, and other atherosclerotic disease events similarly in nondiabetic CHD patients with and without the metabolic syndrome. However, because CHD patients with the metabolic syndrome were found to be at a higher absolute risk than those without it, the benefit from simva-
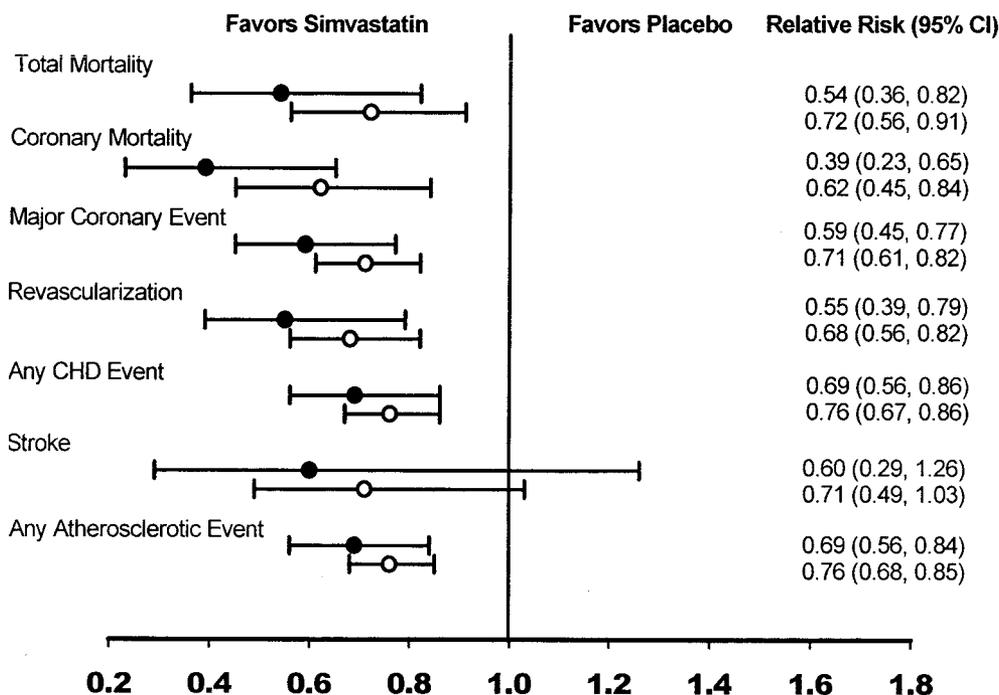


| | Relative Risk (95% CI) |
|---|---|
| Total Mortality | 0.54 (0.36, 0.82) |
| | 0.72 (0.56, 0.91) |
| Coronary Mortality | 0.39 (0.23, 0.65) |
| | 0.62 (0.45, 0.84) |
| Major Coronary Event | 0.59 (0.45, 0.77) |
| | 0.71 (0.61, 0.82) |
| Revascularization | 0.55 (0.39, 0.79) |
| | 0.68 (0.56, 0.82) |
| Any CHD Event | 0.69 (0.56, 0.86) |
| | 0.76 (0.67, 0.86) |
| Stroke | 0.60 (0.29, 1.26) |
| | 0.71 (0.49, 1.03) |
| Any Atherosclerotic Event | 0.69 (0.56, 0.84) |
| | 0.76 (0.68, 0.85) |

**Figure 2—***Effect of simvastatin treatment on relative risk rates (95% CIs) in nondiabetic CHD patients with (●) or without (○) the metabolic syndrome. The Cox proportional hazard model included treatment (simvastatin or placebo), subgroup (with or without metabolic syndrome), treatment-by-subgroup interaction term, age stratification (<60 or ≥60 years), and sex. The treatment-by-subgroup interaction term was not significant (P > 0.12) for each event type.*

statin treatment, in terms of absolute risk reduction, was greater in the subgroup of patients with the metabolic syndrome.

In our study, we used the NCEP definition of the metabolic syndrome but modified it by the use of a BMI cutoff of $\geq 30$ kg/m$^2$ as a substitute for the NCEP sex-specific waist circumference criteria for obesity, because waist circumference measurement was not included in the baseline examination of the 4S. Experience from another study indicates that using this BMI criterion instead of the NCEP waist circumference criteria leads to some underestimation in the proportion of patients satisfying the obesity criterion (7). This underestimation would, however, bias toward the null, thus reinforcing the validity of the results. By the modified NCEP definition, 22.7% of the nondiabetic 4S patients had the metabolic syndrome. The lower prevalence of the metabolic syndrome in the 4S patients than in the corresponding age-group of the general population of the U.S. (5,8) is probably mainly explained by the lower prevalence of obesity in the Northern European countries. Among the 4S patients, hypertension, elevated triglyceride level, and low HDL cholesterol level were the most frequent individual components contributing to the presence of the metabolic syndrome, and of the combinations of three or more components leading to the diagnosis of the syndrome, the following three were the most common: hypertension, high triglyceride level, and low HDL cholesterol level; hypertension, low HDL cholesterol level, and impaired FPG; and hypertension, high triglyceride level, and impaired FPG. The relatively low NCEP cutoff for hypertension ($\geq 130/85$ mmHg) explains, in part, the extremely high prevalence of hypertension among the 4S patients.

Previous subgroup analyses of the 4S data have already shown that the benefit from simvastatin treatment, in terms of relative risk reduction in the risk of CHD events, is similar in CHD patients with individual risk characteristics included in the metabolic syndrome—in patients with previous history of hypertension (18), elevated triglyceride level, low HDL cholesterol level (19,20), or impaired FPG (21)—as in patients without these risk characteristics. In a recent 4S subgroup analysis, the influence of low HDL cholesterol and elevated triglycerides on the response to simvastatin treatment was

assessed by defining these lipid abnormalities by the lowest HDL cholesterol quartile ($<1.00$ mmol/l) and the highest triglyceride quartile ($>1.80$ mmol/l), which are comparable to the corresponding NCEP cutoffs (22). Patients with high LDL cholesterol but with low HDL cholesterol and elevated triglycerides defined by these cutoffs (lipid triad) had increased prevalence of other risk characteristics associated with the metabolic syndrome (increased BMI, hypertension, and diabetes) and a higher CHD event rate than patients with isolated LDL cholesterol elevation (those in the highest HDL cholesterol and lowest triglycerides quartiles). Simvastatin treatment was found to produce a more marked reduction in the risk of CHD events in the subgroup with the lipid triad, expressed as both relative and absolute risk reduction, than in the subgroup with isolated LDL cholesterol elevation.

We excluded patients with diabetes (history of previously diagnosed diabetes or FPG $\geq 7.0$ mmol/l) from the present subgroup analyses. This was done with the recognition of the importance of the metabolic syndrome and the underlying insulin resistance as a background factor for type 2 diabetes and as a contributor to the high CHD risk in people with type 2 diabetes. Another reason for excluding patients with diabetes was the potential confounding effect of diabetes treatments on markers of the metabolic syndrome, particularly triglyceride and glucose levels. In fact, 61% of the 483 excluded diabetic patients had the metabolic syndrome. Diabetic patients with CHD are considered to be at a particularly high risk of death and recurrent CHD events, irrespective of the presence of the metabolic syndrome. In a separate analysis of the nondiabetic CHD patients in the 4S placebo group only, the predictive value of the metabolic syndrome with regard to cardiovascular disease events (a major CHD event or a combined end point of fatal or nonfatal MI or stroke) was almost as high as that associated with the presence of diabetes (15).

The percent changes in LDL cholesterol, triglyceride, and HDL cholesterol levels induced by simvastatin treatment were similar in patients with or without the metabolic syndrome after 1 year and at the study end. These lipid improvements with simvastatin treatment most likely account for a major proportion of

the reduction in recurrent cardiovascular disease events in patients with the metabolic syndrome as well as in patients without it. In the whole 4S cohort, the reduction in CHD events in the simvastatin-treated group was strongly related to the total and LDL cholesterol level achieved during the treatment, less so to the HDL cholesterol level, and not related to triglyceride level during treatment (20).

The main limitation of our study is that it is based on post-hoc subgroup analyses of a study population with both CHD and markedly elevated total cholesterol and LDL cholesterol levels. Furthermore, the 4S was not powered to evaluate the effects of simvastatin treatment on the rates of CHD events and other cardiovascular disease events in the subgroups of those with or without the metabolic syndrome. Yet, it may be noted in this context that the results of the present subgroup analyses were remarkably consistent with regard to all different end points analyzed. It is important to note that our findings on simvastatin treatment effects in CHD patients with the metabolic syndrome participating in the 4S may not be generalizable to CHD patients with different baseline characteristics and to people who are free of cardiovascular disease.

In conclusion, nondiabetic CHD patients with or without the metabolic syndrome realize from simvastatin treatment a similar, substantial reduction in the risk of death, recurrent CHD events, and other atherosclerotic events. The absolute benefit may be greater in patients with the metabolic syndrome, because they are at a higher absolute risk.

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